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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61K 9/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 93/25187</b> <b>(43) International Publication Date:</b> 23 December 1993 (23.12.93)
<b>(21) International Application Number:</b> PCT/US93/05639 <b>(22) International Filing Date:</b> 11 June 1993 (11.06.93) <b>(30) Priority data:</b> 07/897,733 12 June 1992 (12.06.92) US <b>(60) Parent Application or Grant</b> <b>(63) Related by Continuation</b> US 897,733 (CIP) Filed on 12 June 1992 (12.06.92) <b>(71) Applicant (for all designated States except US):</b> ALCON SURGICAL, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134 (US).		<b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> McLAUGHLIN, Richard, N. [US/US]; 2700 Pomponesett Drive, Arlington, TX 76017 (US). LORENZETTI, Ole, J. [US/US]; 1945 Berkeley Place, Fort Worth, TX 76110 (US). <b>(74) Agents:</b> COPELAND, Barry et al.; Alcon Surgical, Inc., 6201 South Freeway, Fort Worth, TX 76134 (US). <b>(81) Designated States:</b> AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> COMBINATIONS OF VISCOELASTICS FOR USE DURING SURGERY  <b>(57) Abstract</b>  Systems for performing surgery, especially ophthalmic surgery, utilizing multiple viscoelastic agents with differing physico-chemical properties are disclosed. The systems enable the skilled surgeon to perform certain steps of a surgical procedure with viscoelastic agents that are particularly well suited for such steps.		

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## COMBINATIONS OF VISCOELASTICS FOR USE DURING SURGERY

### Cross-Reference to Related Application

This application is a continuation-in-part of U.S. Application Serial No. 07/897,733, filed June 12, 1992, and entitled "The Use of Combinations of  
5 Viscoelastics During Surgery," now pending.

### Background of the Invention

There are known viscous or viscoelastic agents for ophthalmic surgical use (hereinafter "agent" or "viscoelastic agent"), for example, the VISCOAT® product (Alcon Surgical, Inc.), which contains sodium hyaluronate and chondroitin sulfate;  
10 Healon® and Healon® GV (Kabi Pharmacia), Amvisc® and Amvisc Plus® (IOLAB), and Vitrax® (Allergan), all of which contain essentially pure sodium hyaluronate; and Occucoat® (Storz), which contains hydroxypropylmethylcellulose (HPMC). All of these highly purified products are useful in certain ocular surgical procedures, such as cataract surgery. They are used by the skilled ophthalmic surgeon for  
15 several surgical purposes, including maintenance of intraocular spaces, protection of ophthalmic tissues, particularly corneal endothelial cells, and as an aid in manipulating ophthalmic tissues. These agents are generally viscous enough to permit the skilled surgeon to use them for their intended surgical purposes, but not so viscous that expression of the agent through a cannula of acceptable bore size  
20 might be made difficult.

There is, however, no one viscoelastic agent which best fulfills all of the surgical purposes. Due to their particular physical characteristics, certain viscoelastic agents will be better suited for particular aspects of the surgical procedure. For example, in cataract surgery, the combination of relatively low  
25 molecular weight sodium hyaluronate and chondroitin sulfate found in the

VISCOAT® product works extremely well in maintaining the anterior chamber during capsulotomy, or anytime during the cataract procedure, and in adhering to and protecting tissues, particularly the corneal endothelium. However, due to its adhering and coating characteristics, the VISCOAT® product is more difficult to remove from the anterior chamber of the eye than some other agents. In addition, although it can be used to manipulate tissue for insertion of an intraocular lens (IOL) into the eye, certain other agents are known to perform this function better.

Viscoelastic solutions of relatively high molecular weight sodium hyaluronate having functionally desirable viscosity, such as Healon® or the PROVISC™ product (Alcon Laboratories, Inc.), are highly cohesive, but relatively non-adherent with respect to the tissues they may contact during surgery. These characteristics make such solutions well suited for use as a soft tool for the gentle manipulation of delicate tissues during surgery. For example, these viscoelastic agents can be used to inflate the capsular bag and facilitate the insertion of an IOL. Their cohesiveness and lack of adhesiveness also make them easier to remove from the eye at the end of surgery. However, sodium hyaluronate is not as effective as some agents in protecting ophthalmic tissues, especially during phacoemulsification procedures.

HPMC adheres well to ophthalmic tissues and therefore protects them, but does not perform as well as, for example, the VISCOAT® product, in maintaining the anterior chamber, or as well as sodium hyaluronate in manipulating tissues. However, it can be easily diluted with irrigation fluid following IOL implantation. The removal of the viscous or viscoelastic agent at the close of surgery may help to prevent intraocular pressure spikes following surgery.

In general, viscous solutions containing relatively higher molecular weight agents, including high molecular weight sodium hyaluronate, are more effective in maintaining the intraocular space than less viscous solutions containing relatively lower molecular weight agents; however, the high molecular weight agents tend to

be highly cohesive and may be prematurely aspirated from a surgical site. This may occur, for instance, if they come into contact with the phacoemulsification tip during a phacoemulsification procedure. The relatively lower molecular weight products, which due to their tenacious characteristics adhere to and protect tissues, are more difficult to remove from the surgical site.

It would be advantageous to use a system containing more than one viscoelastic agent during an ophthalmic procedure, such as a cataract operation, to obtain the maximum benefits offered by the variety of available viscoelastic agents. The systems of the present invention provide this advantage.

#### Summary of the Invention

The present invention is directed to systems containing viscoelastic agents with differing physicochemical properties, for use during a surgical procedure, particularly ophthalmic surgery. The systems are employed during ophthalmic surgery in order to achieve satisfactory intraocular space maintenance and ocular tissue protection, and to provide for manipulation of ocular tissues and ease of removal of the viscoelastic agents at the end of the procedure. An object of the invention is to provide systems comprising viscoelastic agents possessing different cohesive or adherent properties. Such systems enable the skilled surgeon to use viscoelastic agents exhibiting a relatively greater degree of cohesiveness for certain steps of a surgical procedure, and to use a more adherent viscoelastic agent for other steps in the same procedure. The surgeon is thereby afforded the benefit of the use of multiple viscoelastic agents, each of which is particularly well suited for certain steps of the procedure.

#### Detailed Description of the Invention

The systems of the present invention comprise multiple viscoelastic agents having different adherent or cohesive properties, which multiple agents are for use

in a single surgical procedure. Those skilled in the art will recognize that the systems of the present invention can be employed by the skilled surgeon in a variety of surgical procedures that may be improved by alternately choosing agents with the desired characteristics to either help manipulate tissues or to function as an adherent protective agent. The preferred systems are useful in ophthalmic surgery.

Viscoelastic agents which are useful for the systems of the present invention include but are not limited to: sodium hyaluronate, chondroitin sulfate, polyacrylamide, HPMC, proteoglycans, collagen, methylcellulose, carboxymethyl cellulose, ethylcellulose, polyvinylpyrrolidone and keratan, all of various molecular weights and concentrations, or combinations thereof. Those skilled in the art will appreciate that the suitability of a given agent for a particular step in a surgical procedure will depend upon such things as the agent's concentration, average molecular weight, viscosity, pseudoplasticity, elasticity, rigidity, adherence (coatability), cohesiveness, molecular charge, and osmolality in solution. The agent's suitability will depend further on the function(s) which the agent is expected to perform and the surgical technique being employed by the surgeon.

For portions of surgical procedures involving phacoemulsification and/or irrigation/aspiration, it is generally preferable to use a viscoelastic agent that possesses relatively greater adherent properties and relatively lesser cohesive properties. Such viscoelastic agents are referred to herein as "adherent" agents. The cohesiveness of a viscoelastic agent in solution is thought to be dependent, at least in part, on the average molecular weight of that agent. At a given concentration, the greater the molecular weight, the greater the cohesiveness. The adherent agents, which are relatively lacking in cohesiveness, therefore will typically be of lower molecular weight; the molecular weight will typically be less than 1,000,000 daltons, preferably less than 750,000 daltons. To achieve a functionally desirable viscosity, the concentrations of the lower molecular weight agents in solution will need to be relatively higher than for higher molecular weight

agents. These concentrations will typically be at least about 2% weight to volume (e.g. Occucoat®). The VISCOAT® product, for example, contains approximately 4% chondroitin sulfate (~ 25,000 daltons) and 3% sodium hyaluronate (~ 700,000 daltons). Vitrax® is believed to contain approximately 3% sodium hyaluronate (~ 500,000 daltons). For agents such as these, which are being employed primarily for protective purposes as opposed to tissue manipulation purposes, a functionally desirable viscosity will be a viscosity sufficient to permit a protective layer of such agent to remain on the tissue or cells of concern during the surgical step(s) being performed. Such viscosity will typically be from about 3,000 cps to about 60,000 cps (at shear rate of 2 sec<sup>-1</sup> and 25° C), and preferably will be about 40,000 cps. Such adherent agents are capable of providing the protective function previously discussed, yet are not prone to inadvertent removal, which could jeopardize the delicate tissue being protected.

Those portions of surgical procedures involving manipulation of delicate tissue are generally better served by viscoelastic agents that possess relatively greater cohesive properties and relatively lesser adherent properties. Such agents are referred to herein as "cohesive" agents. Typically, these cohesive agents will possess average molecular weights in excess of 1,000,000 daltons and will have functionally desirable viscosity at concentrations of not more than about 1.6% weight to volume. Examples of such cohesive agents are: the PROVISC™ product, Healon®, Healon® GV, Amvisc® and Amvisc Plus®. For cohesive agents such as these, which are being employed primarily for tissue manipulation or maintenance purposes as opposed to protective purposes, a functionally desirable viscosity will be a viscosity sufficient to permit the skilled surgeon to use such agent as a soft tool to manipulate or support the tissue of concern during the surgical step(s) being performed. Such viscosity will depend upon the average molecular weight of the agent and its concentration in solution. Most preferred are cohesive agents having an average molecular weight of at least about 2,000,000 daltons and a concentration in solution of between about 1.0 to about 1.4% weight to volume. Such cohesive agents are capable of maintaining intraocular space and



manipulating tissue without adhering to it. When their purpose has been served, they can, because of their cohesive properties, be readily removed with minimal trauma to the surrounding tissue.

In a preferred system for cataract surgery, one viscoelastic agent is used during capsulotomy, expression or phacoemulsification of the cataractous lens, and irrigation/aspiration (Stage 1), and a different viscoelastic agent is used following extraction of the lens and during implantation of an IOL (Stage 2). The agent used during Stage 1 of the surgery should be adherent enough to be retained in the anterior chamber so as to protect the delicate endothelial cells. Preferably, a sufficient volume of the solution containing the Stage 1 agent should be available to fill and maintain anterior chamber space. Approximately 0.3 to 0.5 mL is typically utilized for this purpose. Most preferably, the solution of the Stage 1 agent should exhibit sufficient viscosity to at least partially relieve lens convexity, i.e., flatten the lens somewhat so that a capsulotomy can be performed with more control and less chance of peripheral capsular tearing. The primary purpose of the adherent agent is to protect the tissues, particularly the corneal endothelial cells, from trauma resulting from shear forces and direct contact from instruments during the capsulotomy and from nuclear fragments during removal of the cataractous lens.

The cohesive agent, used during Stage 2, should effectively allow for implantation of an IOL by facilitating the manipulation of tissue, i.e., filling and opening the capsular bag in which the IOL will be placed, and should also maintain the anterior chamber prior to and during implantation of the IOL. It should also be relatively easy to remove from the eye after IOL implantation.

Thus, the system of the invention, as preferably used in cataract surgery, would consist of the following steps: surgically opening the eye; filling the anterior chamber with an adherent agent for use in Stage 1; performing a capsulotomy; removing any cataractous tissue; filling the capsular bag with a cohesive agent for use in Stage 2; and implanting an IOL in the capsular bag. The skilled surgeon will

generally remove all or part of the cohesive agent, the adherent agent, or both, subsequent to implantation of the IOL in the capsular bag.

The preferred system for cataract surgery comprises an adherent agent containing sodium hyaluronate and chondroitin sulfate for use during Stage 1 of a procedure, and a cohesive agent containing a relatively high molecular weight sodium hyaluronate agent for use during Stage 2. Most preferably the adherent agent utilized during Stage 1 agent will contain approximately 4% chondroitin sulfate (~ 25,000 daltons) and 3% sodium hyaluronate (~ 700,000 daltons) and will have a viscosity of approximately 40,000 cps (at a shear rate of 2 sec<sup>-1</sup> and 25° C) as found in the VISCOAT® product. The most preferred adherent agent for use during Stage 2 will consist of essentially pure sodium hyaluronate having an average molecular weight greater than about 2,000,000 daltons and a concentration of about 1.0% to about 1.4% weight to volume, as found in the PROVISCO™ product, Healon® and Healon® GV. The Stage 1 adherent agent is to be used upon the surgeon's entrance into the anterior chamber. The purpose of this agent is to fill and maintain the chamber and protect the tissues during capsulotomy, phacoemulsification and/or irrigation/aspiration and removal of the cataractous lens elements. The Stage 2 cohesive agent is then introduced into the empty capsular bag to inflate it for introduction and placement of an IOL. During its introduction, the high molecular weight sodium hyaluronate may partially displace the VISCOAT® product and in that manner supplement the maintenance of the corneal dome. Alternatively, some of the VISCOAT® product may be removed by the surgeon prior to the introduction of the Stage 2 cohesive agent. Upon completion of IOL placement the Stage 2 agent can be removed readily with irrigation/aspiration techniques known to those skilled in the art. Such removal may help prevent a sharp post surgical increase in intraocular pressure. The use of these two agents during cataract surgery provides for optimal maintenance of the anterior chamber, protection of tissues, and manipulation of the capsular bag for IOL implantation.

The present invention may also be used in corneal transplant surgery. In conjunction with the removal of the patient's corneal button, it is desirable to replace the aqueous humor with a highly viscous agent that will provide a firm bed to support the donor cornea, yet be susceptible to easy removal upon completion of the surgery. The donor graft, on the other hand, requires maximum protection from the surgical trauma and should therefore be coated with a different, more adherent agent. Thus, a system of the invention may be utilized in corneal transplant surgery in the following manner. Upon removing the patient's corneal button, the aqueous humor is replaced, in total or in part, with a highly viscous, highly cohesive agent, such as the high molecular weight sodium hyaluronate of the PROVISC<sup>TM</sup> product or Healon® GV. The donor graft is carefully removed from its storage medium and coated with an adherent agent, such as the VISCOAT® product or HPMC. In addition, the contact portions of any instrument used to handle the donor graft may be coated with the adherent agent prior to such handling. The donor cornea is then placed on the bed created by the cohesive agent, and sutured into place. The cohesive agent may be evacuated from the eye just prior to completion of the transplant, or immediately thereafter by known methods.

A system of the present invention may also be used in posterior segment surgery. In a retinal detachment procedure, for example, a highly viscous, cohesive agent such as the PROVISC<sup>TM</sup> product or Healon® GV will be used to manipulate the retina into position against the basement membrane of the choroid. Small amounts of an adherent agent, such as the VISCOAT® product, may be injected behind the retina before or after such manipulation to temporarily maintain the contact between the retina and basement membrane while more permanent attachment procedures well known to those skilled in the art are performed (e.g. tacking or laser welding).

It will be appreciated that the different viscoelastic agents for use in the present invention may be maintained in separate or common containers.

Preferably, the system will consist of two such agents, which are conveniently packaged together. In a preferred embodiment, an adherent agent, such as the VISCOAT® product, and a cohesive agent, such as the PROVISC™ product, will be packaged together in a single, sterile package for the surgeon's convenience.

5 In such a common package, the agents may be contained in separate vials or syringes, or loaded into a common vial or syringe. In either configuration, it may be desirable to use one or more agent that has been stained with a pharmacologically acceptable dye or otherwise marked, so that the different agents may be more readily distinguished by the surgeon during use.

10 Neither the type of packaging nor the specific means by which the agents are administered are critical to this invention, the scope of which is intended to include any assortment, collection, kit or product which encompasses, teaches or suggests using multiple viscoelastic agents in a single surgical procedure.

15 Moreover, it is to be understood that various modifications and substitutions to the system described herein can be made by those skilled in the art without departing from the spirit and scope of this invention.

What is claimed is:

1. A system for use in performing a surgical procedure in humans, comprising a first viscoelastic agent and a second viscoelastic agent, said first viscoelastic agent having greater adherent properties than said second viscoelastic, and said  
5 second viscoelastic agent having greater cohesive properties than said first viscoelastic agent.
2. A system according to claim 1, wherein the first viscoelastic agent and the second viscoelastic agent are commonly packaged.
3. A system according to claim 2, wherein the first viscoelastic agent and the  
10 second viscoelastic agent are in separate containers within the common package.
4. A system according to claim 2, wherein the first viscoelastic agent and second viscoelastic agent are contained in a single container within the common package.
5. A system according to claim 2, wherein at least one of the first viscoelastic  
15 agent and second viscoelastic agent is marked to permit visual differentiation during use.
6. A system according to claim 5, wherein at least one of the first viscoelastic agent and second viscoelastic agent is marked with a pharmacologically acceptable dye.
7. A system according to claim 1, wherein the first and second viscoelastic  
20 agents are independently selected from the group consisting of: sodium hyaluronate, chondroitin sulfate, polyacrylamide, collagen, methylcellulose, ethylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, polyvinyl pyrrolidone, keratan, and combinations thereof.

8. A system according to claim 7, wherein the system is adapted for use in ophthalmic surgery.

9. A system according to claim 8, wherein the first viscoelastic agent has a viscosity from about 3,000 to about 60,000 cps.

5 10. A system according to claim 9, wherein the first viscoelastic agent comprises a combination of sodium hyaluronate and chondroitin sulfate.

11. A system according to claim 10, wherein the viscosity of the first viscoelastic agent is about 40,000 cps.

10 12. A system according to claim 11, wherein the second viscoelastic agent has an average molecular weight of greater than about 1,000,000 daltons.

13. A system according to claim 12, wherein the second viscoelastic agent comprises sodium hyaluronate.

14. A system according to claim 13, wherein the average molecular weight of the second viscoelastic agent is greater than about 2,000,000 daltons.

15 15. A system according to claim 7, wherein the first viscoelastic agent comprises a combination of sodium hyaluronate at a concentration of approximately 3% weight to volume and chondroitin sulfate at a concentration of approximately 4% weight to volume, and wherein the second viscoelastic agent comprises sodium hyaluronate at a concentration of approximately 1.0% weight to volume.

16. A system according to claim 15, wherein the sodium hyaluronate of the first viscoelastic agent has an average molecular weight of less than 1,000,000 daltons, the chondroitin sulfate of the first viscoelastic agent has a molecular weight of about 25,000 daltons, and the sodium hyaluronate of the second viscoelastic agent has an average molecular weight of greater than 2,000,000 daltons.

17. The use of an adherent first viscoelastic agent and a cohesive second viscoelastic in conducting ophthalmic surgery in a human eye having delicate tissues and intraocular spaces, comprising: coating and protecting the delicate tissues with the first viscoelastic agent; and manipulating the delicate tissues with the second viscoelastic agent.

18. The use of an adherent first viscoelastic agent and a cohesive second viscoelastic agent as in claim 17, further comprising maintaining intraocular space with said second viscoelastic agent.

19. The use of an adherent first viscoelastic agent and a cohesive second viscoelastic agent in conducting cataract surgery in a human eye having an anterior chamber, a posterior chamber and a capsular bag located within the posterior chamber, comprising:

surgically opening the eye;  
filling the anterior chamber with the first viscoelastic agent;  
performing a capsulotomy;  
removing any cataractous tissue;  
filling the capsular bag with the second viscoelastic agent; and  
implanting an intraocular lens in the capsular bag.

20. The use according to claim 19, further comprising removing the second viscoelastic agent from the capsular bag after the intraocular lens has been implanted in the capsular bag.

21. The use according to claim 19, wherein the first viscoelastic agent  
5 : comprises a combination of sodium hyaluronate and chondroitin sulfate.

22. The use according to claim 19, wherein the second viscoelastic agent comprises sodium hyaluronate.

23. A system for use in performing a surgical procedure, comprising a first viscoelastic agent and a second viscoelastic agent, said first viscoelastic agent  
10 comprising a combination of approximately 3% weight to volume sodium hyaluronate having an average molecular weight of less than 1,000,000 daltons, and approximately 4% weight to volume chondroitin sulfate having an average molecular weight of approximately 25,000 daltons, and said second viscoelastic agent comprising approximately 1.0% weight to volume sodium hyaluronate  
15 having an average molecular weight of at least 2,000,000 daltons.



## INTERNATIONAL SEARCH REPORT

PCT/US 93/05639

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (several classification symbols apply, indicate all)<sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/00

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>7</sup>

Classification System	Classification Symbols
Int.Cl. 5	A61K ; A61L

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched<sup>8</sup>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X,Y	EP,A,0 244 178 (IOLAB INC.) 4 November 1987 see claims 1-4 see column 3, line 3 - line 29 ---	1-14
Y	US,A,4 141 973 (ENDRE A. BALASZ) 27 February 1979 see claims 1,2 ---	1-14
X	WO,A,8 903 205 (UNIVERSITY OF FLORIDA) 20 April 1989 see claims 1-15 see page 6, line 33 - page 7, line 18 see page 10, line 28 - page 11, line 2 see page 23; example 7 ---	1-9
X	US,A,4 819 617 (EUGENE P. GOLDBERG ET AL.) 11 April 1989 see claims 1-4,14,15 ---	1-8
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<sup>10</sup> Special categories of cited documents:

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"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

18 AUGUST 1993

Date of Mailing of this International Search Report

31. 08. 93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

VENTURA AMAT A.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0 136 782 (CILCO INC.) 10 April 1985 see claims 1-3 -----	1-8

## INTERNATIONAL SEARCH REPORT

international application No.

PCT/IS 93/05639

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
**REMARK: Although claims 17-22 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the composition.**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# ANNEX THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9305639  
SA 75780

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on  
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0244178	04-11-87	AU-B- 604236	13-12-90
		AU-A- 7211787	03-12-87
		JP-A- 63022013	29-01-88
US-A-4141973	27-02-79	None	
WO-A-8903205	20-04-89	US-A- 4965253	23-10-90
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		JP-T- 2500253	01-02-90
		JP-B- 4031713	27-05-92
US-A-4819617	11-04-89	None	
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		JP-C- 1537013	21-12-89
		JP-A- 60056922	02-04-85